Reply to:
Current DMOAD options for the treatment of osteoarthritis

Sirs,

We appreciate the letter from Dr Yeap and the opportunity to respond. As clearly stated in our review the focus was on describing "the state of the field for disease-modifying pharmacologic agents that are in late-stage development-specifically phase 2/3". As neither of the agents that you mention fall into that category, it was not appropriate to include them in the review.

Neither of the agents highlighted by Dr Yeap, glucosamine and strontium ranelate, have been approved for disease modification in osteoarthritis (OA). If Dr Yeap feels inclined to use these agents in her patients, hopefully she does so with appropriate clinical judgement cognisant of some of the reasons why regulators have not approved either agent for this indication.

The most commonly used complementary medicine in knee OA is glucosamine. In randomised control trials, glucosamine has a similar effect to placebo on pain, with industry independent trials showing smaller effects than commercially funded ones (1, 2). The GAIT study, which is an NIH-funded RCT demonstrated that glucosamine was not significantly better than placebo in reducing knee pain by 20% (3). Our own recent meta-analysis demonstrated that symptom benefits from glucosamine were not of a clinically meaningful magnitude (4). Evidence for a possible structure modifying effect remains controversial (5) and most recent guidelines do not advocate for their use in this context (6-9).

We completely agree that the findings of the Servier trial assessing the efficacy of strontium ranelate (SR) were exciting when they were first published (10). The trial randomly allocated 1683 patients to three treatment groups (strontium ranelate 1g [n=558] or 2g/day [n=566] or placebo [n=559]). The primary endpoint was radiographic change in JSW (medial tibiofemoral compartment) over 3 years *versus* placebo. Treatment with SR for over 3 years was associated with significant beneficial effects on knee structure (slowing radiographic progression) at a dose of 1 or 2 g/day and on symptoms (reducing knee pain) at a dose of 2 g/day in patients with knee OA. It does demonstrate clearly that disease modification is possible and the outcomes on both radiological and clinical progression of knee osteoarthritis appear to be of clinical significance (10). However, as Dr Yeap is no doubt aware from reference number seven included in her letter, Servier is no longer manufacturing strontium ranelate because of concerns over cardiovascular safety and specifically thromboembolic side effects. The reference cited by Dr Yeap from the EMA appropriately suggests that this agent "only be used by people for whom there are no other treatments for osteoporosis". Given the length of time required for administration of strontium to have a therapeutic effect in OA, the frequency with which cardiovascular contraindications including ischaemic heart disease and hypertension occur in persons with OA and the lack of an approved OA indication from regulatory agencies it does not seem sensible to advocate for the use of strontium in this context.

While there are undoubtedly challenges in getting disease-modifying drugs across the line for regulatory agencies, we don't think we should expose our patients unnecessarily to harm or mislead them with our clinical advice.

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Competing interests: D. Hunter is on the consultant advisory board for Merck Serono, TLCBio, Pfizer and Lilly;
W.M. Oo has declared no competing interests.

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